ATX-559, a First in Class DHX9 Inhibitor, and Targeted Therapeutic for Molecularly Defined Tumors with Genomic Instability and Replicative Stress

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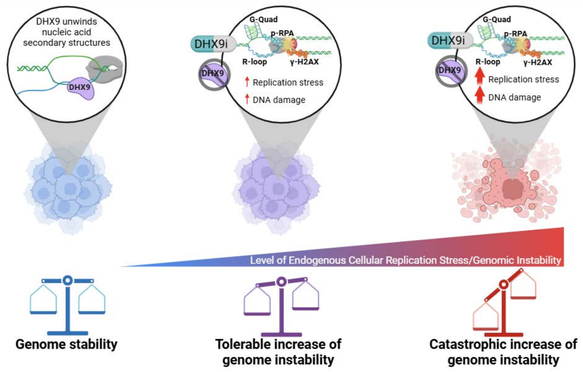
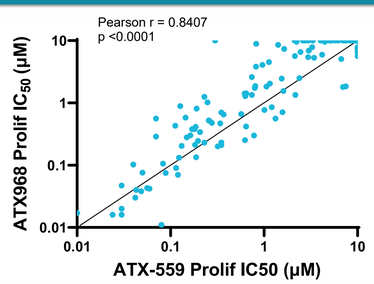
RNA Helicase DHX9 Plays an Important Role in Maintaining Genome Stability



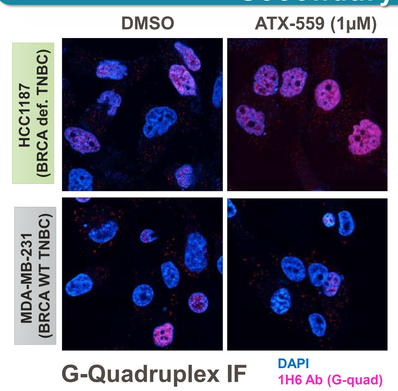
- DHX9 is a multi-functional RNA helicase, and contributes to genome stability by unwinding nucleic acid secondary structures, including DNA/RNA hybrids (R-loops), circular RNA and G-quadruplexes[1,2,3]
- Selective dependance on DHX9 has been observed in molecularly defined tumors that exhibit genomic instability and elevated replication stress
- We previously demonstrated that DHX9 genetic loss or inhibition by the DHX9 tool compound ATX968 was efficacious in tumors with defective mismatch repair and/or high microsatellite instability (dMMR/MSI-H), or with alterations in the DDR genes BRCA1 and/or BRCA2 (BRCA)[4,5,6]
- **Here we describe ATX-559, a potent, selective, orally bioavailable, small-molecule inhibitor of DHX9 helicase activity that is currently in clinical development**

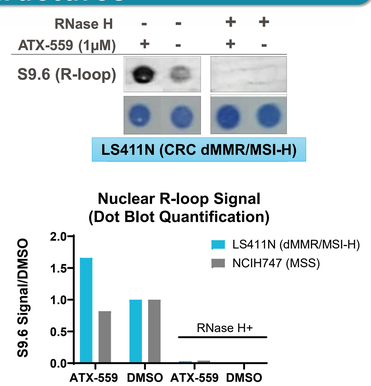
ATX-559 Cellular Potency Correlates Well to Tool DHX9 Inhibitor ATX968

- Inhibition of DHX9 by the clinical candidate ATX-559 demonstrates slightly greater cellular potency than the DHX9 tool compound ATX-968, and fully recapitulates its associated biological effects
- Correlation plot depicts anti-proliferative IC_{50} values across a panel of 165 cancer cell lines

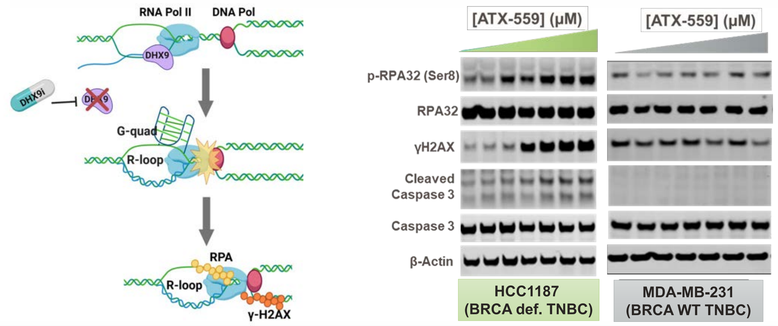


DHX9 Inhibition by ATX-559 Results in Selective Accumulation of Aberrant Nucleic Acid Secondary Structures

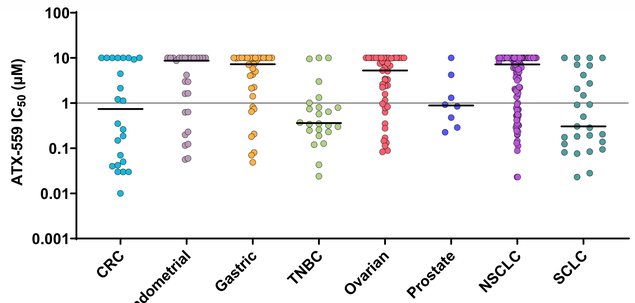




DHX9 Inhibition by ATX-559 Leads to Replication Stress, DNA Damage and Apoptosis

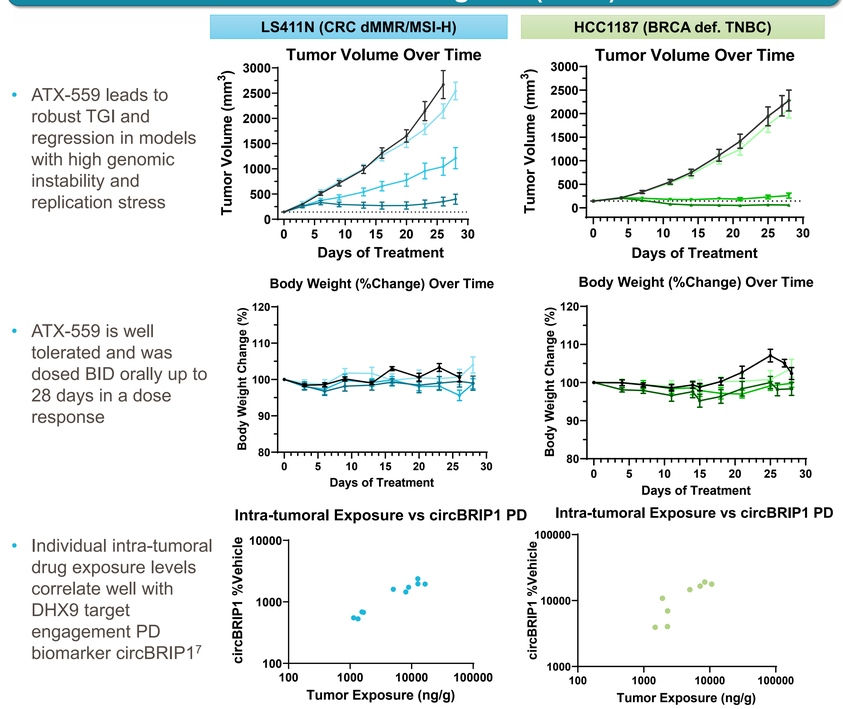


ATX-559 Exhibits Robust Anti-Proliferative Activity In Cancer Cell Lines from Multiple Indications



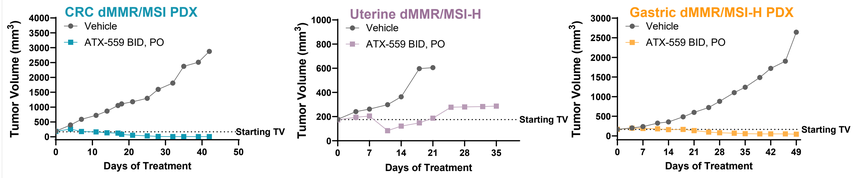
ATX-559 Dose-Dependent Tumor Growth Inhibition in Cell Line-Derived Xenograft (CDX) Models

- ATX-559 leads to robust TGI and regression in models with high genomic instability and replication stress
- ATX-559 is well tolerated and was dosed BID orally up to 28 days in a dose response
- Individual intra-tumoral drug exposure levels correlate well with DHX9 target engagement PD biomarker circBRIP1[7]

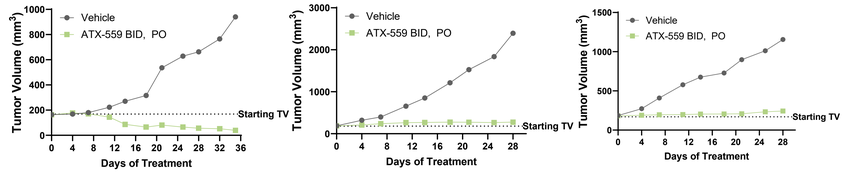


ATX-559 Displays Robust Anti-Tumor Activity in a Panel of Patient-Derived Xenograft (PDX) Models

dMMR/MSI-H (CRC, Endometrial and Gastric) PDX Tumors



BRCA Deficient Breast PDX Tumors



Conclusions

- DHX9 is a novel therapeutic target in cancers that exhibit genomic instability and elevated replicative stress, such as dMMR/MSI and BRCA deficient tumors
- ATX-559 is a potent, selective first-in-class oral DHX9 inhibitor which results in selective accumulation of unresolved R-loops and G-quadruplexes further increasing replication stress and genomic instability in these vulnerable tumors leading to irreparable DNA damage, cell cycle arrest[6] and ultimately cell death
- ATX-559 is well tolerated in vivo, leading to robust and dose dependent tumor growth inhibition and regression in BRCA deficient breast cancer and dMMR/MSI-H CDX and PDX models
- **ATX-559 is currently under investigation in a first-in-human, Phase 1/2, open-label, dose-escalation and expansion study (NCT06625515),** with a focus on advanced or metastatic patients with BRCA-1 and/or BRCA-2-deficient breast cancer or MSI-H and/or dMMR solid tumors. Additional undisclosed solid tumor indications under replicative stress and representing significant patient populations have the potential to be explored either in parallel to the initial indications or in subsequent studies

References

[1]Lee and Pelletier, Oncotarget (2016)
[2]Chakraborty et al, Nature Comm (2021)
[3]Gulliver et al, Future Science (2020)
[4]Castro et al, Cancer Res (AACR 2023) 83 (7)
[5]Castro et al, Cancer Res (AACR 2024) 84 (1)
[6]Castro et al, Cancer Res; 85(4) 2025
[7]Brennan et al, Cancer Res (AACR 2024) 84 (6)

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